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3 Claims

[Claim 1]

Pharmaceutical agents containing active form vitamin D derivatives and bisphosphonates as active ingredients for the treatment or prevention of osteoporosis.

[Claim 2]

Pharmaceutical agents described in claim 1 for the treatment or prevention of osteoporosis, wherein the active form vitamin D derivatives are one or combination of multiple compounds selected from a group of compounds consisted of :

1 α -hydroxy-vitamin D; 1 α , 24-dihydroxy-vitamin D; 1 α , 25-dihydroxy-vitamin D; 1 α , 24, 25-trihydroxy-vitamin D; 24, 24-difluoro-1 α , 25-dihydroxy-vitamin D; 26, 26, 26, 27, 27, 27-hexafluoro-1 α , 25-dihydroxy-vitamin D.

[Claim 3]

Pharmaceutical agents described in claim 1 or 2 for the treatment or prevention of osteoporosis, wherein the bisphosphonates are one or combination of multiple compounds selected from a group of compounds consisted of :

*allendronic acid; *vamidronic acid; *etydronic acid, *tyrdronic acid, and *lysedronic acid.

**Spelling of the names of bisphosphonates listed above are created from the pronunciation in Japanese; note that there is no difference between "L" and "R", "B" and "V" in Japanese pronunciation.*

A Comment from the translator:

Although vitamin D3 is not specifically claimed in claims, 1 α -vitamin D3 was used in the examples. It appears that the phrase "active form vitamin D derivatives" was meant to generically cover vitamin D subtypes.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] the active vitamins D by which this invention is used for a prevention or treatment of osteoporosis, and a ***** phon -- it is related with the medicine which contains acids as an active principle

[0002]

[Description of the Prior Art] By the small intestine, active vitamins D, such as 1alpha-hydroxy vitamin D 3 (1alpha-OH-D3) and 1alpha, 24(R)-dihydroxy vitamin D 3 and 1alpha, and 25-dihydroxy vitamin D 3, have an absorption promotion operation of calcium, and to the bone, since it has an operation of adjusting a bone resorption and an osteogenesis, they are used as a therapeutic drug of the morbus which begins osteoporosis and is based unusually [various calcium metabolisms]. However, at the point of the enhancement in bone density and a bone intensity, although the treatment agent which makes these active vitamins D an active principle was almost satisfactory, it had the fault that the side effect that a patient's calcium concentration in blood is raised arose.

[0003] on the other hand -- a ***** phon -- acids act specifically to the activated osteoclast, are considered to suppress a bone resorption by suppressing the activity, and are used as a therapeutic drug of the morbus which begins osteoporosis and is based unusually [a calcium metabolism]

[0004] however, a ***** phon -- although there was no side effect that a patient's calcium concentration in blood was raised unlike the treatment agent by which the treatment agent which makes only acids an active principle makes the above-mentioned active vitamins D an active principle, at the point of the enhancement in bone density and a bone intensity, it was the treatment agent which makes the above-mentioned active vitamins D an active principle

[0005]

[Problem(s) to be Solved by the Invention] Then, it aims at offering the medicine with which this invention persons can raise bone density and a bone intensity as a treatment agent of osteoporosis more than these conventionally well-known treatment agents, an EQC, or it, and the calcium concentration in blood does not rise. Moreover, it aims at this invention persons offering the medicine with which a fall of bone density and a bone intensity can be suppressed, and the calcium concentration in blood does not rise as a preventive of osteoporosis.

[0006]

[Means for Solving the Problem] the active vitamins D conventionally used independently, respectively when this invention persons inquired zealously about the effective component as a treatment agent of osteoporosis, and a ***** phon -- it is enabled to offer the osteoporosis treatment agent which maintained the balance of not raising the enhancement in bone density and a bone intensity, and calcium concentration in blood by using acids together furthermore -- according to a research of this invention persons -- the above-mentioned active vitamins D and a ***** phon -- it is enabled it not only to raise the lowered bone density and the lowered bone intensity, but to find out having the effect which suppresses a fall of bone density and a bone intensity, and to offer an osteoporosis preventive by using acids together

[0007] namely, this invention -- active vitamins D and a ***** phon -- it is the osteoporosis preventive

or treatment agent which contains acids as an active principle

[0008] Hereafter, this invention is explained in detail.

[0009] As active vitamins D used by this invention, it is distinguished from the vitamin D which does not have a physiological function in itself, the vitamin D which has physiological functions, such as calcium and a bone metabolic-regulation operation, is said, and an active vitamin D 2, the active vitamins D 3, and those derivatives are included. As the example, it is 1alpha-hydroxy vitamin D, 1alpha, 24-dihydroxy vitamin D, 1alpha, 25-dihydroxy vitamin D, alpha [1] and 24, 25-trihydroxy vitamin D, 24, and 24-difluoro, for example. - It is 1alpha, 25-dihydroxy vitamin D, 26, 26, 26, 27 and 27, and 27-hexafluoro. - 1alpha, 25-dihydroxy vitamin D, etc. are mentioned. Especially, 1alpha-hydroxy vitamin D 3 and 1alpha, 24(R)-dihydroxy vitamin D 3 and 1alpha, and 25-dihydroxy vitamin D 3 are desirable. Moreover, as active vitamins D in this invention, you may be a kind of these, or two sorts or more of mixture, and the mixed rate is defined suitably.

[0010] As dose of these active vitamins D, it is an amount effective in a prevention or treatment of osteoporosis, and when using as a treatment agent generally although there is no ***** since it is based on the modality of a patient's age, weight, and combined use treatment, the frequency of the treatment, the modality of effect desired, or the prescribing [a medicine / for the patient] method, it will usually be [day] 0.1micro g-20microg/day preferably 0.01micro g-100microg /. In the case of a medicine for external application, it will usually be [day] 20microg/day from 1microg preferably 0.01micro g-100microg /. When using as a preventive, it will usually be [day] 0.1micro g-0.5microg/day preferably 0.05micro g-5microg /.

[0011] the ***** phon used by this invention -- as acids, an allene ***** acid, a ***** acid, the etidronic acid, a chill ***** acid, and a ***** acid can be illustrated An allene ***** acid is desirable especially. Moreover, even if these are kinds, they may mix and use two or more sorts at an arbitrary rate.

[0012] a ***** phon -- since it is based on the modality of a patient's age, weight, and combined use treatment, the frequency of the treatment, the modality of effect desired, or the prescribing [a medicine / for the patient] method, although it is an amount effective in a prevention or treatment of osteoporosis as dose of acids, and there is no ***** generally, when using as a treatment agent generally, 5mg - 400mg /will usually be [day] 10mg - 200mg/day preferably In the case of a medicine for external application, it will usually be [day] 20microg/day from 1microg preferably 0.01micro g-100microg /. When using as a preventive, 1mg - 10mg /will usually be [day] 2 or 5mg - 5mg/day preferably.

[0013] the osteoporosis preventive or treatment agent of this invention -- these active vitamins D and a ***** phon -- although it can mix and they can also be simultaneously prescribed for the patient that what is necessary is just what contains acids as an active principle, each can also be separately prescribed for the patient continuously

[0014] Moreover, the number of times of medication per day of the osteoporosis preventive of this invention or a treatment agent can be performed in 1 time or 2 - 3 steps.

[0015] prescribing a medicine for the patient continuously, before bone density etc. decreases greatly here, in using ** of this invention as a preventive -- desirable -- especially -- a ***** phon -- acids -- it is desirable to prescribe a medicine for the patient in the order of -> active vitamins D It is desirable to perform simultaneous medication on the other hand, in using ** of this invention as a treatment agent.

[0016] Moreover, it not only can raise bone density and a bone intensity, but the osteoporosis preventive or treatment agent of this invention does not raise the calcium concentration in blood. When a well-known osteoporosis treatment agent, i.e., active vitamins D, is conventionally used as an active principle, this Although it has the effect in respect of enhancement by bone density and the bone intensity, it has the side effect that the calcium concentration in blood rises. on the other hand -- a ***** phon, when only acids are used as an active principle It compares, although there was no side effect that the calcium concentration in blood rose and the effect was inadequate in respect of the enhancement in bone density and a bone intensity. the osteoporosis preventive or treatment agent of this invention active vitamins D and a ***** phon -- by using together two kinds with the different action mechanism of acids as an active

principle It has the characteristic feature at the point which enabled it to offer the medicine which maintained the balance which has the enhancement effect of a well-known osteoporosis treatment agent, an EQC or the bone density beyond it, and a bone intensity conventionally, and does not have this side effect. [0017] moreover, the active vitamins D of this invention and a ***** phon -- acids can be tablet-ized by well-known technique with those suitable excipients that see or are explained below As an example of such a pharmaceutical form, oral agents, such as an elastic capsule, hard capsules, a tablet, and the syrup, the injection, or a medicine for external application can be mentioned.

[0018] As such an excipient, oily ester, such as vegetable oil (for example, the corn oil, cotton seed oil, a coconut oil, an almond oil, and peanut oil are mentioned) and a medium-chain-fatty-acid glyceride, straight mineral oil, vaseline, an animal fat and oil, a cellulosic (for example, a crystalline cellulose, hydroxypropylcellulose, the hydroxypropyl methylcellulose, and a methyl cellulose are mentioned), a polyvinyl pyrrolidone, a dextrin, a lactose, a mannitol, a sorbitol, starch, etc. are mentioned. Moreover, additives, such as an antioxidant, a wetting agent, a viscosity stabilizer, and a coloring agent, can also be added if needed.

[0019] Specifically, oral agents, such as a preventive of the osteoporosis of this invention or an elastic capsule of a treatment agent, a tablet, and a granule for dry syrup, can be manufactured by the technique indicated by JP,57-45415,B, JP,63-46728,B, JP,63-60007,B, and JP,61-87619,A.

[0020]

[Embodiments of the Invention] Hereafter, an example is given and explained about this invention.

[0021]

[The example 1 and the examples 1-3 of a comparison] The ovariectomy was given to the rat (a Sprague-Dawley system, female) of 40 week-old. After it left it for 15 weeks and bone quantity decreased, internal use of them was carried out for 12 weeks by independent or combined use as an allene ***** acid disodium salt (dosage weight of 0.2mg/kg) and 1alpha-hydroxy vitamin D 3 (0.02microg [/kg] dosage weight, "one alpha in drawing", and notation) were shown below. The rat was euthanized after the medication end, the centrum was isolated, and the bone density (g [BMD and]/cm²) of the 4-6th centurms (L4-L6) was measured by the double energy X-ray absorption method. The result was shown in drawing 1.

Example of comparison 1; ovariectomy group (control)

an example of example of comparison 2; allene ***** acid medication group comparison 3; one alpha medication group example -- as for the example 1, as compared with the examples 1-3 of a comparison, the enhancement in bone density was checked from 1; allene ***** acid + one alpha combined use group view 1

[0022]

[The examples 2 and 3 and the examples 4-6 of a comparison] The ovariectomy was given to the rat (a Sprague-Dawley system, female) of 48 week-old. The medicine for 20 or less weeks was prescribed for the patient as shown below from the next day before bone quantity and a bone intensity carry out decrement start.

Example of example of comparison 4; ovariectomy group (control); vehicle comparison 5; allene ***** acid medication group; allene ***** acid disodium salt (dosage weight of 0.5mg/kg)

Example of comparison 6; one alpha medication group; 1alpha-hydroxy vitamin D 3 (dosage 0.05 mug/kg weight)

Example 2; one alpha -> allene ***** acid medication group; 1alpha-hydroxy vitamin D 3 (dosage 0.05 mug/kg weight)

(Ten weeks) -> allene ***** acid disodium salt (dosage weight of 0.5mg/kg) (ten weeks)

Example 3; allene ***** acid -> one alpha medication group; allene ***** acid disodium salt (dosage weight of 0.5mg/kg)

(Ten weeks) -> 1alpha-hydroxy vitamin D 3 (dosage 0.05 mug/kg weight) (ten weeks)

the rat after a medication end is euthanized -- making -- a lumbar vertebrae -- isolating -- a double energy X-ray absorption method -- the bone density (g [BMD and]/cm²) of the 3rd lumbar vertebrae (L3) --

moreover, the maximum load (N) was measured with the centrum compression test. The result was shown in the drawing 2 and the drawing 3. Furthermore, the calcium concentration in a blood serum was shown in drawing 4.

[0023] Examples 2 and 3 showed the decrement depressor effect of the bone density of an equivalent lumbar vertebrae, and a bone intensity (maximum too heavy more measurement) as compared with the examples 4-6 of a comparison. The passage clear from the drawing 2 and the drawing 3. Moreover, when examples 2 and 3 were compared, bone density and the bone intensity improved from the group which the direction of the group which prescribed the example 3, i.e., an allene ***** acid, for the patient in early stages medicated with one alpha in early stages.

[0024] Moreover, the passage clear from drawing 4, compared with the examples 4-6 of a comparison, calcium concentration in a blood serum is pressed down low, and examples 2 and 3 became clear [that there is no side effect].

[0025]

[Effect of the Invention] The osteoporosis preventive or treatment agent of this invention is a medicine which maintained the balance which bone density and a bone intensity can be raised as a treatment agent of osteoporosis more than these conventionally well-known treatment agents, an EQC, or it, and is the medicine with which the balance not going up was able to take the calcium concentration in blood, and can suppress a fall of bone density and a bone intensity also as a preventive of osteoporosis further, and does not go up the calcium concentration in blood.

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CLAIMS

[Claim(s)]

[Claim 1] active vitamins D and a ***** phon -- the osteoporosis preventive which contains acids as an active principle, or a treatment agent

[Claim 2] the osteoporosis preventive according to claim 1 which are a kind or two sorts or more of active vitamins D as which active vitamins D are chosen out of the group which consists of 1alpha-hydroxy vitamin D, 1alpha, 24-dihydroxy vitamin D, 1alpha, 25-dihydroxy vitamin D, alpha [1] and 24, 25-trihydroxy vitamin D, 24, 24 *****-1alpha, 25-dihydroxy vitamin D, 26, 26, 26, 27 and 27, and 27-hexafluoro-1alpha and 25-dihydroxy vitamin D, or a treatment agent

[Claim 3] a ***** phon -- a kind as which acids are chosen out of the group which consists of an allene ***** acid, a ***** acid, the etidronic acid, a chill ***** acid, and a ***** acid, or two sorts or more of ***** phons -- the osteoporosis preventive according to claim 1 or 2 which is acids, or a treatment agent

[Translation done.]

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